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THE SPECTRUM OF BENIGN TO MALIGNANT LYMPHOPROLIFERATION IN SJÖGREN'S SYNDROME

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SUMMARY

Clinical and pathological evidence suggests that a wide spectrum of lymphoproliferation exists in Sjögren's syndrome (SS), from benign disease with lymphoid infiltrates confined to glandular tissue on the one end, to widespread lymphoreticular malignancy on the other. In the middle of the spectrum are patients threatened by extraglandular extension of lymphoproliferation which is not clinically or histologically malignant and which apparently has the potential to regress with appropriate therapy or to progress to frank neoplasia. Illustrative patients are described. Over thirty other case reports associating SS with pseudolymphoma, Waldenstrom's macroglobulinaemia, reticulum cell sarcoma, or other lymphomas appear in the literature. Similar lymphoproliferative processes have been observed in other autoimmune diseases, in certain immune deficiency states, with hydantoin and other anticonvulsant drugs, and in experimental animal models. In SS, as in these other conditions, it seems likely that a combination of genetic, immunologic, and viral or other unknown environmental factors plays a role in pathogenesis.

INTRODUCTION

Lymphoid infiltration is a prominent feature of Sjögren's syndrome. In this autoimmune disease usually affecting middle-aged women, components of the sicca complex (keratoconjunctivitis sicca and xerostomia) are associated, in half the patients, with rheumatoid arthritis or another connective tissue disease (Bloch *et al.*, 1965; Talal, 1966). Hypergammaglobulinaemia, rheumatoid factor, antinuclear antibodies, and other autoantibodies occur frequently (Bunim *et al.*, 1964). The major symptoms of dry eyes and dry mouth result from glandular tissue destruction associated with lymphocytic crowding of the lacrimal and salivary glands. Less common symptoms of vaginal dryness and chronic bronchitis may also be due to lymphoid infiltration of glandular elements in the genital and upper respiratory tracts.

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In some patients with SS, lymphoproliferation is not confined to glandular tissue but becomes more generalized to involve regional lymph nodes or distant sites such as nodes, lung, kidney, spleen, bone marrow muscle, or liver (Bunim & Talal, 1963; Talal & Bunim, 1964; Talal, Sokoloff & Barth, 1967). When such 'extraglandular' lymphoproliferation occurs, diagnosis is often difficult, and clinically and histologically the disease may simulate or be indistinguishable from frankly malignant lymphoproliferative disorders such as Waldenstrom's macroglobulinaemia, reticulum cell sarcoma, or other lymphomas. Since the subsequent clinical course is frequently that of the lymphoma, ending fatally, the early recognition of extraglandular lymphoproliferation in SS and prompt institution of appropriate therapy are important.

Patients with coexisting SS and extraglandular lymphoproliferation reported in the literature to date are reviewed below, and our personal experience with this problem updated. Analogous lymphoproliferation associated with other connective tissue diseases, with immune deficiency states, with anticonvulsant drugs, and with certain animal models are also discussed.

THE BENIGN LOCAL LYMPHOEPITHELIAL LESION

The classic histopathologic lesion of SS (Morgan & Castleman, 1953) is infiltration of glandular tissue by lymphocytes and plasma cells. As the disease progresses, lymphoid cells crowd the glands, with destruction of acini and occasional germinal follicle formation. In spite of acinar destruction, ductal epithelial cells proliferate, eventually forming the so-called 'epimyoepithelial islands'.

The ductal cell proliferation is noteworthy for two reasons. First, the earliest lymphocytic infiltration in the salivary gland is periductal in distribution. Second, an antisalivary duct antibody (Bertram & Halberg, 1964; MacSween *et al.*, 1967) is often present in the serum. This antibody is specific for salivary ducts (Feltkamp & van Rossum, 1968) and is the first evidence of organ-specific sensitization in SS. The stimulus which renders the ductal epithelial cells antigenic in SS remains unknown. There is some evidence that circulating lymphocytes in SS are sensitized to salivary gland tissue (Soborg & Bertram, 1968; Bertram & Soborg, 1970). Possibly the initial infiltrating lymphoid cells are attracted into the salivary glands because they are sensitized to a ductal antigen. The elaboration of soluble factors from such sensitized lymphocytes may attract other nonsensitized lymphoid cells to the gland.

The lower lip contains numerous minor (accessory) salivary glands that become involved with the same process of lymphocytic infiltration and glandular destruction that occurs in the major glands in SS. Immunoglobulin synthesis studies utilizing lip biopsy material have shown that the infiltrating cells produce excess quantities of IgG, IgM, and IgA (Talal, Asofsky & Lightbody, 1970). The most distinctive excess involves IgM. In half of the patients with SS, immunoglobulin produced by lip lymphoid cells has anti-IgG or rheumatoid factor activity (Anderson *et al.*, 1971). Production of an IgM paraprotein has been demonstrated in lip biopsies from three patients with coexisting Waldenstrom's macroglobulinaemia and SS.

In patients with 'benign' SS, then, there is considerable evidence of active immunologic activity: (1) the prominence of lymphocytic infiltration of glandular tissue in the benign lymphoepithelial lesion; (2) the presence of hypergammaglobulinaemia in half the patients and the high incidence of autoantibodies in general (Bunim *et al.*, 1964); (3) the presence of

an organ-specific autoantibody (antisalivary duct); and (4) the local excess synthesis of immunoglobulins, especially of macroglobulins, some with autoantibody activity.

EXTRAGLANDULAR LYMPHOPROLIFERATION ('PSEUDOLYMPHOMA')

In the majority of patients with SS, significant lymphoproliferation apparently remains confined to salivary and lacrimal tissue, resulting in a chronic benign course of stable or progressive xerostomia and xerophthalmia. In some, however, after even 15 years or more of benign disease, there appears evidence of extension of lymphoproliferation to extraglandular sites. The clinical manifestation of such extraglandular spread depends upon the nature of the infiltrating lymphoid cells and the organs involved.

The extraglandular lymphoid infiltrates are of two general types. They may be highly pleomorphic and include small and large lymphocytes, plasma cells, and large reticulum cells. In a lymph node the cells may distort the normal architecture and extend beyond the capsule, making the diagnosis between a benign and malignant lesion very difficult. The term 'pseudolymphoma' has been applied when the lesions show tumour-like aggregates of lymphoid cells but do not meet histologic criteria for malignancy (Talal *et al.*, 1967). PAS-positive intranuclear inclusions and macroglobulins may be present, as in Waldenstrom's macroglobulinaemia. The other type of infiltrate involves histologically malignant cells and will be discussed in the next section.

In pseudolymphoma, the site of extraglandular lymphoproliferation determines the clinical presentation. There may be hyperplasia of lymph nodes near salivary glands, and striking regional lymphadenopathy may be the predominant clinical feature. On the other hand, lymphoid infiltration may be excessive in a single distant organ such as kidney or lung which may become functionally impaired, giving rise to renal abnormalities or pulmonary insufficiency. Renal tubular acidosis may arise through such a mechanism (Kaltreider & Talal, 1969). Occasionally lymphoproliferation may be more generalized and mimic advanced lymphoma with generalized lymphadenopathy, pulmonary infiltration, and constitutional symptoms such as fever and weight loss, as in patient L.B.R., reported earlier (Talal & Bunim, 1964). The following patients illustrate pseudolymphoma presenting as localized adenopathy or organ failure:

Case 1. *M.R.* (08-14-61)

This 48-year-old white woman had a 20-year history of dry eyes and dry mouth. Episodic swelling of the parotid gland with extreme redness, heat, and pain began on the right in 1960 and on the left in 1968. In late 1968, right parotid enlargement became persistent and she developed cervical adenopathy.

On Clinical Center admission in April 1969, the right parotid gland was large and firm with numerous large, firm cervical lymph nodes. There was no other significant adenopathy. The white blood count (WBC) was 5,500 with 12% lymphocytes and 9% monocytes. The erythrocyte sedimentation rate (ESR) was 38. Rheumatoid factor titre by bentonite flocculation test (BFT) was 1:128. Total protein was 8·4 g%, with 1·5 g% γ-globulin. Schirmer's test was abnormal, salivary flow was absent, and the parotid was not visualized on scanning with technetium 99m. Lower lip biopsy demonstrated nodular infiltrates of lymphocytes consistent with SS. Biopsies of the right parotid gland and right cervical lymph

nodes both showed diffuse lymphoreticular hypercellularity, predominantly reticulum cell, with obliteration of the normal architecture. Chest film and renal fuction were normal. The diagnosis was localized pseudolymphomatous changes in the parotid glands and regional lymph nodes.

The patient was treated with 3000 rads to the anterior neck including both cervical and both parotid regions, with shrinking of the nodes and parotid glands to near normal size. Subsequently, on no further treatment, she has done well without recurrent adenopathy or parotid swelling.

Case 2. *R.G.* (07-13-34)

This 59-year-old white woman developed mouth dryness in 1965, followed within a year by the onset of eye dryness, bilateral tender parotid swelling, and arthralgia. Rheumatoid factor titre was 1:1280. Biopsies of the left parotid gland and left submandibular lymph node demonstrated lymphoid infiltration compatible with SS.

On Clinical Center admission in 1967, salivary flow was low, sialogram demonstrated bilateral sialectasis, salivary gland scanning demonstrated diminished radioisotope uptake, and lower lip biopsy revealed lymphocytic infiltration typical for SS. Keratoconjunctivitis sicca was present. In March 1968 the patient developed a lower extremity rash on the legs with skin biopsy evidence of acute necrotizing vasculitis. In April 1968, in the absence of new symptoms, liver and renal function tests first became abnormal with SGOT rise to 155 and with the appearance of microscopic haematuria and pyuria, proteinuria, azotemia (BUN 30 mg%), and fall in creatinine clearance to 43 ml/min LE preparations and anti-DNA antibodies continued to be negative. The patient had excreted an acid load normally in May 1967, but repeat testing in October 1968 demonstrated latent renal tubular acidosis and vasopressin-resistant hyposthenuria. Liver function tests returned to normal, but renal function worsened. In May 1969 creatinine clearance was 33 ml/min and urinary protein was 1·5 g/24 hr. Open renal biopsy showed massive lymphocytic and plasmacytic interstitial infiltration with nodular concentrations of cells, tubular degeneration, moderate glomerular basement membrane thickening, and necrotizing arteriolitis (Kaltreider & Talal, 1969). The glomeruli were normal on fluorescence microscopy.

In June 1969 treatment was instituted with cyclophosphamide, 100 mg daily. Within a month proteinuria cleared completely, creatinine clearance rose to 50 ml/min, and BUN and creatinine fell to within normal limits. With her white blood count maintained in the 3000–4500 range on cyclophosphamide doses between 50 and 100 mg daily, the patient has subsequently done well with stable renal function and normal urinary sediment. While she has had no further parotid swelling, xerostomia and xerophthalmia persist on cyclophosphamide.

Other cases of nonmalignant, extraglandular lymphoproliferation in SS have been reported in addition to the previous six patients observed at this institute (Talal *et al.*, 1967). Tkac, Kvetensky & Vesely (1967) described a patient with SS, hypergammaglobulinaemia, purpura, hepatomegaly, and an IgG paraprotein which disappeared on corticosteroid therapy. Sage & Forbes (1968) reported a patient with SS, autoimmune haemolytic anaemia, hepatosplenomegaly, and abnormal bone marrow and peripheral lymphocytosis, with improvement on azathioprine.

Features that should alert the clinician to the possibility of extraglandular lymphoproliferation in a patient with SS are regional or generalized lymphadenopathy, hepato-

splenomegaly, pulmonary infiltrates, renal insufficiency, purpura, leucopenia, hypergammaglobulinaemia, or elevated serum macroglobulin. The entity of 'pseudolymphoma' cannot be clearly defined but occupies the middle portion of the spectrum of lymphoproliferation in SS, merging with benign disease (e.g. with hypergammaglobulinaemic purpura) on the one end, and with frankly malignant disease such as Waldenstrom's macroglobulinaemia or reticulum cell sarcoma on the other. The diagnosis may be difficult and requires a histologically benign lymphoid infiltrate, which often poses the pathologic dilemma of distinguishing hyperplasia from neoplasia.

MALIGNANT LYMPHOPROLIFERATION

The other type of extraglandular lymphoid infiltrate is histologically malignant, enabling the specific diagnosis of a lymphoproliferative neoplasm. These lesions may also appear after several years of apparently benign disease, may or may not be preceded by histologically benign infiltrates, and are often highly resistant to therapy.

The most common malignant lymphoproliferation in SS is a highly undifferentiated reticulum cell sarcoma or unclassifiable primitive or stem cell lymphoma. At least two patients have progressed from 'pseudolymphoma' to fatal malignancy. The earlier course of disease in both patients has previously been described in detail (Talal *et al.*, 1967). After 9 years of apparently benign SS, A.S. (NIH 05-59-68) developed cervical and supraclavicular adenopathy (Fig. 1), with a later biopsy diagnosis of pseudolymphoma. Although she did well on no treatment for 6 years, in August 1966 she presented with progressive adenopathy, weight loss, and fever. Serum IgM had fallen from 0·8 to 0·2 mg/ml (normal 1·2), with decline in rheumatoid factor titre from 1:1024 to negative. Cervical lymph node biopsy now revealed frank reticulum cell sarcoma. In spite of deep cobalt radiotherapy, cyclophosphamide, vincristine, and prednisone therapy, she died in December 1966. At post-mortem examination there was widespread reticulum cell sarcoma with involvement of practically every organ. The tumour consisted of large sheets of noncoherent, immature histiocytes (Fig. 1).

The other patient, H.H. (06-39-59), had been treated for pseudolymphoma (diagnosed by cervical node biopsy) with phenylalanine mustard. Lymphadenopathy, hepatosplenomegaly, and cryoglobulinaemia disppeared and serum macroglobulin decreased from 13·4 to 2·9 mg/ml. Phenylalanine mustard was discontinued in 1966. In December 1968 the patient noted fatigue and weight loss and became dyspneic with bilateral pleural effusions. The cryomacroglobulinaemia had returned, and LE cells were present for the first time. Her disease progressed rapidly, and she died in January 1969. Post-mortem examination demonstrated a malignant lymphoproliferative disorder, type unclassified, of lymph nodes and bone marrow. Involved organs showed nearly complete replacement with pleomorphic primitive cells which were not classifiable as differentiated lymphoid, plasma, or reticulum cells.

Another patient was referred to the Clinical Center in the terminal phase of a malignant lymphoproliferation accompanying SS:

Case 3. *M.B.* (08-04-43)

This 48-year-old white woman noted the onset of dry eyes and parotid swelling in 1951. In 1956 she received radiation therapy (500 R) to the right parotid. In 1957 a scalene node biopsy demonstrated a benign lymphoid infiltrate. Steroid treatment was begun. Keratitis

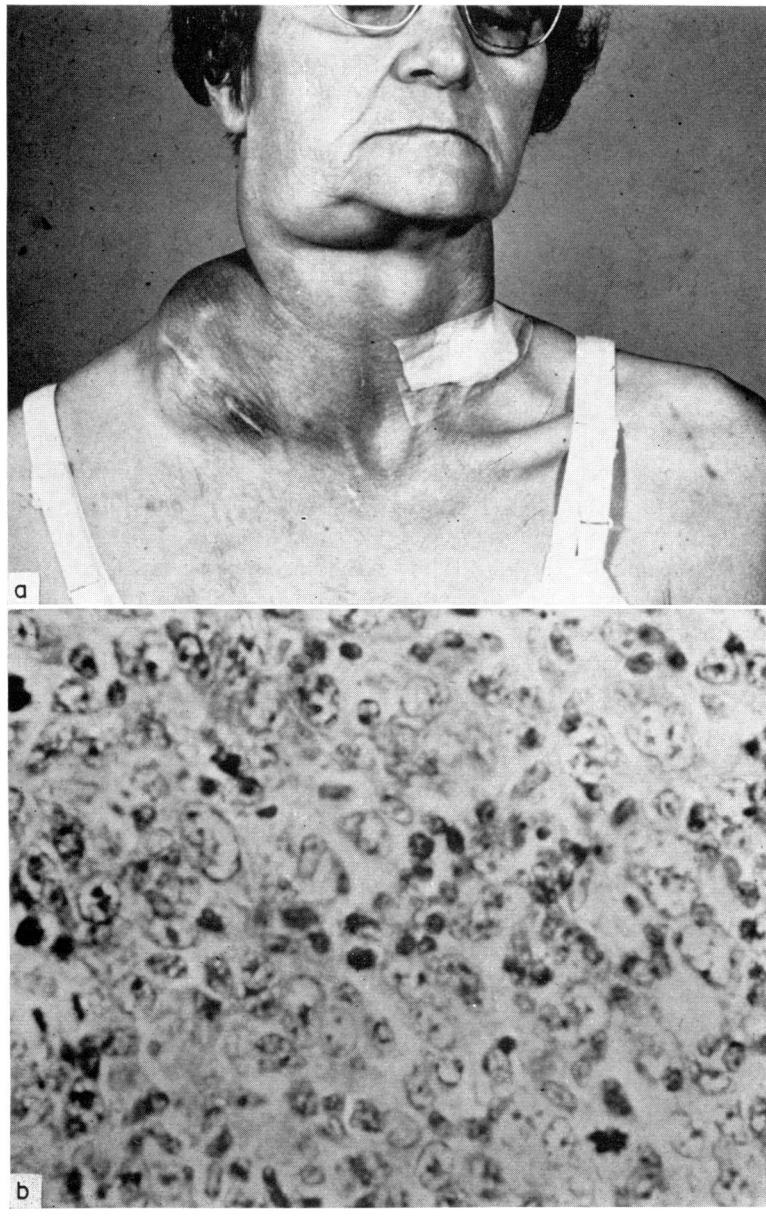

FIG. 1. (a) Lymphadenopathy in a patient (A.S.) with Sjögren's syndrome. The adenopathy had waxed and waned for 6 years, with four lymph node biopsies demonstrating pseudolymphoma, but the lesion progressed to malignancy. (b) Cervical lymph node biopsy at this time showed reticulum cell sarcoma. Haematoxylin and eosin stain. (Original magnification ×540.)

sicca was diagnosed in 1964 by a positive Schirmer test, filamentary keratitis, and corneal staining. Because of recurrent swelling, further radiation therapy (100 R to each parotid) was administered in 1966. In March 1968 she was found to have cervical adenopathy with radiologic evidence of hilar and superior mediastinal masses. Another scalene node biopsy showed a pleomorphic lymphoid infiltrate. Bronchoscopy demonstrated a narrowed right upper lobe orifice. She received 600 R to the anterior mediastinum and another 300 R to the right parotid in April 1968, a further 100 R to the submandibular nodes in July, and 100 R to the neck in October. In November 1968 she developed sudden right facial palsy with marked right parotid swelling and loss of voice, with radiologic evidence of increased superior mediastinal and hilar masses and the appearance of a right upper lobe infiltrate.

On referral to the Clinical Center in December 1968, the patient was chronically and acutely ill with fever, cervical adenopathy, and respiratory distress. She had lymphopenia (WBC 4,800 with 1% lymphocytes) and hypogammaglobulinaemia (total protein 5·0 g% with 0·5 g% gammaglobulin). IgM was 0·3 mg/ml. Rheumatoid factor titre was 1:128. Left supraclavicular lymph node biopsy demonstrated a lymphoma of uncertain type. About 95% of the cells were normal reticulum cells with no evidence of frank reticulum cell sarcoma. She underwent tracheostomy and received 800 R to the mediastinum and extensive antibiotic therapy but progressively deteriorated and died.

Post-mortem examination demonstrated masses of enlarged lymph nodes in the area of the right parotid gland and around the trachea and superior vena cava. These nodes contained a polymorphous cellular infiltrate of lymphocytes, atypical plasma cells, and atypical reticulum cells. The pathologic diagnosis was malignant lymphoma, type unclassified.

In addition to the three cases described above, five other cases of coexistent SS and reticulum cell or stem cell sarcoma have been described from this institute (Talal & Bunim, 1964; Talal *et al.*, 1967) and another three case reports have appeared in the literature. Rothman, Block & Hauser (1951) were the first to note this association. Hornbaker, Foster & Williams (1966) described the development of massive splenomegaly after 5 years of sicca symptoms and parotid swelling in a 78-year-old woman who went on to die of disseminated reticulum cell sarcoma. Miller (1967a) reported a 32-year-old woman who had xerostomia and parotid swelling since 1961 and benign lymphoepithelioma on parotid microscopic examination in 1964. The right parotid was irradiated. Later in 1964 she developed keratoconjunctivitis sicca and cervical lymphadenopathy with biopsy demonstration of lymphadenitis. During the next year adenopathy progressed and repeat biopsy revealed reticulum cell sarcoma, treated by irradiation. Another three cases have been reported (Bark & Perzik, 1968; Pinkus & Dekker, 1970) associating extrasalivary reticulum cell sarcoma with benign lymphoepithelial lesion of the parotid gland in patients with parotid swelling but no other apparent features of SS.

A low IgM level may herald the presence or development of malignant lymphoproliferation and is a poor prognostic sign. A fall in serum IgM is often accompanied by a reduction in the rheumatoid factor titre and may precede the onset of generalized hypogammaglobulinaemia. Two of our patients, J.T. (Talal & Bunim, 1964) and A.S., had documented falls in serum γ-globulin concomitant with the appearance of malignancy. A patient with definite SS but low IgM and absent rheumatoid factor is suspect for a neoplastic lymphoproliferative disorder. A patient currently under study at our institute illustrates the point:

Case 4. *T.J.* (08-18-39)

This 46-year-old white woman in 1963 noted the onset of bilateral submandibular gland enlargement without other symptoms. In 1967 she experienced easy fatigability and weight loss. Her annual chest X-ray was abnormal for the first time, showing extensive nodular and lingular infiltrates throughout both lung fields. A palpable right axillary lymph node was biopsied, demonstrating hyperplasia. Upon hospitalization in September 1967, she was found to have enlarged submandibular glands and cervival, axillary, and femoral adenopathy. An extensive work-up, including bronchoscopy, failed to establish an etiology for her pulmonary disease. Scalene node biopsy demonstrated reactive hyperplasia. Liver biopsy

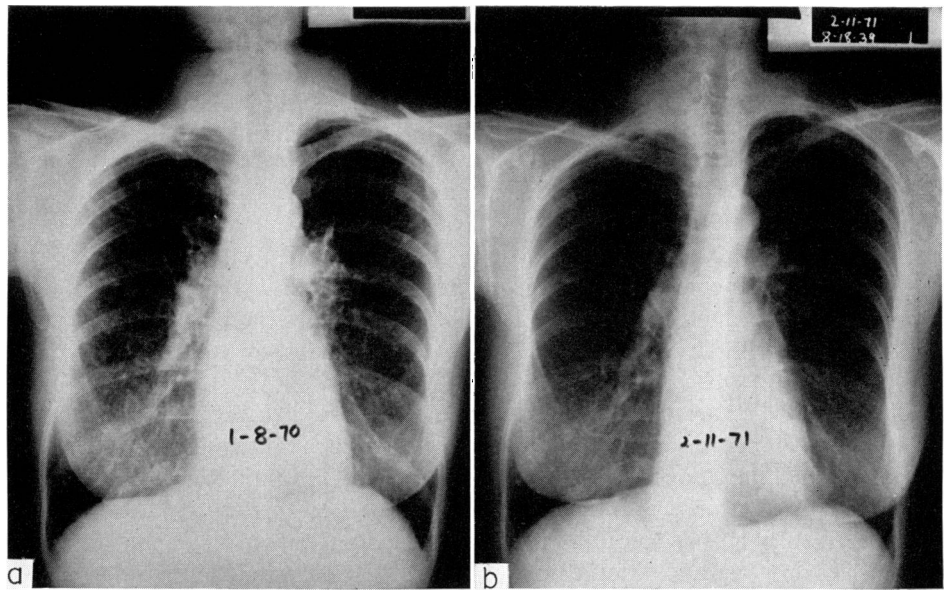

FIG. 2.Case 4. Roentgenograms of the chest. (a) Diffuse interstitial thickening in a patient with Sjögren's syndrome and no respiratory symptoms. A lung biopsy at this time is illustrated in Fig. 3. (b) Improvement after one year of cyclophosphamide therapy.

was normal. In January 1968 she had an episode of herpes zoster of the left intercostal region. In June 1969 she noted the onset of marked dryness of her eyes and mouth. A Schrimer's test was positive.

In November 1969 she was admitted to the Clinical Center. She had severe xerostomia and xerophthalmia but no symptoms of pulmonary disease. Submandibular glands were enlarged and small occipital and supraclavicular nodes were palpable. The WBC was 6,100 with 61% neutrophils, 20% lymphocytes, 6% monocytes, 9% eosinophils and 4% basophils. Total protein was 6·5 g% with 0·6% γ-globulin. Quantitative immunoglobulins were IgM 0·3, IgG 9·7 and IgA 1·05 mg/ml. Bentonite flocculation test for rheumatoid factor was negative. Salivary flow was absent, and there was complete absence of pertechnetate uptake by salivary glands during sequential scintigraphy. A lip biopsy demonstrated lymphocytic infiltration and acinar destruction compatible with SS. Bone marrow aspiration was suggestive of early lymphoproliferative disease with lymphocytosis and

aggregates of lymphocytes. Chest radiograph demonstrated bilateral diffuse interstitial thickening (Fig. 2). Pulmonary function tests indicated resting hyperventilation, but there was no evidence of restrictive ventilatory defect. Diffusion capacity was only slightly decreased. Lymphangiography demonstrated a single enlarged pelvic lymph node and multiple small filling defects in several normal-sized nodes.

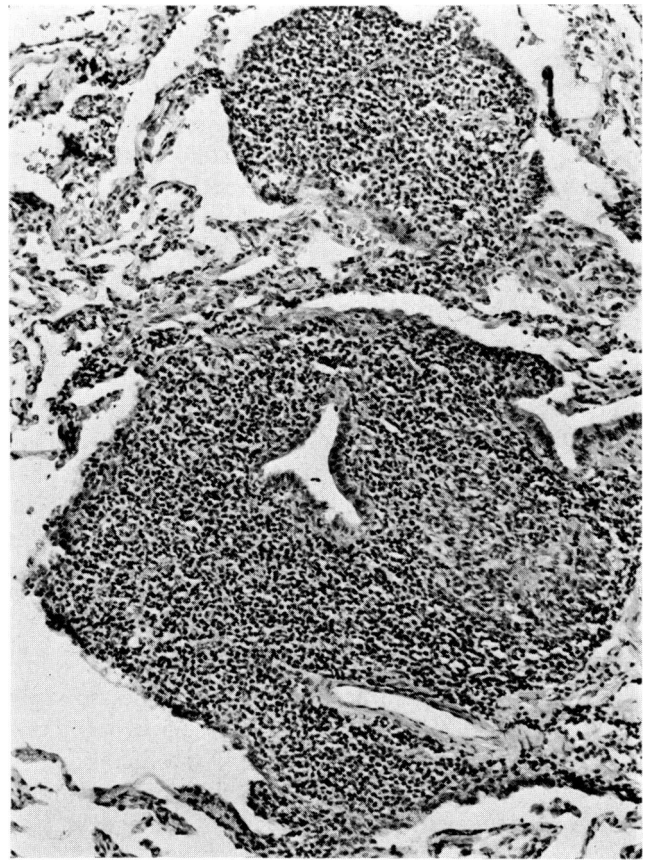

FIG. 3. Case 4. Lung biopsy demonstrating malignant lymphocytic lymphoma, with nodular peribronchiolar lymphocytic infiltrates. Haematoxylin and eosin stain. (Original magnification ×130.)

In January 1970 lymph node biopsy showed loss of normal architecture and diffuse lymphocytic infiltration. In an open lung biopsy there were nodular lymphocytic infiltrates with a peribronchiolar distribution (Fig. 3). Pathologic diagnosis was malignant lymphocytic lymphoma.

In February 1970 cyclophosphamide, 100 mg daily, was instituted. Two months later she noted improvement in her symptoms of xerostomia and xerophthalmia. The submandibular gland swelling had disappeared. In May 1970 repeat technetium scintigraphy demonstrated significantly improved salivary glandular uptake. After one year of treatment chest films

demonstrate improvement (Fig. 2). On cyclophosphamide, 75 mg daily, the patient has continued to do well, with slowly improving lacrimal and salivary glandular function.

A variety of other malignant lymphoproliferative disorders have been noted in association with SS. Lattes (1962) and Dourov *et al.* (1968) reported single cases of coexisting thymoma and SS, and Pinkus & Dekker (1970) described the development of thymoma 3 years following parotid swelling in a 42-year-old woman with benign lymphoepithelial lesions of the parotid glands. Senti *et al.* (1964) reported a case of giant follicular lymphoma with SS. Dameshek (1965) observed lymphosarcoma during the course of a patient with autoimmune haemolytic anaemia and SS. Thorpe (1969) described a 74-year-old woman who presented with polymyalgia rheumatica and then progressed to SS with splenomegaly and progressive lymphadenopathy. Lymph node biopsy established the diagnosis of lymphosarcoma. The development of Hodgkin's disease during the course of SS has been previously cited (Talal & Bunim, 1964). Yoshinaga (1968) reported the development of malignant lymphoma of the vocal cords in a 42-year-old woman with keratoconjunctivitis sicca, xerostomia, and parotid swelling.

The development of neoplasms of both the lymphoid and epithelial components of the parotid glands with benign lymphoepithelial lesions has been observed. Bilder & Hornova (1967) reported the development of lymphosarcoma of the right parotid gland, a rare lesion, in a 76-year-old woman 9 years after the clinical, sialographic, and parotid biopsy diagnosis of SS. Recently, Gravanis & Giansanti (1970) reported malignant courses in three patients with parotid swelling without signs or symptoms of SS but with initially benign lymphoepithelial lesions of the parotid glands. Parotid masses recurred following excision, and regional and even distant metastases appeared, with the histology demonstrating low-grade to poorly-differentiated carcinoma or 'malignant lymphoepithelial lesions'.

WALDENSTROM'S MACROGLOBULINAEMIA

The involvement of macroglobulins in the lymphoproliferative process in SS is noteworthy. The excessive production of IgM in the lip biopsies is at times so striking as to suggest primary macroglobulinaemia even in patients whose serum hypergammaglobulinaemia is polyclonal. In the presence of extraglandular lymphoproliferation, serum IgM levels may be either abnormally low (suggesting development of sarcoma or lymphoma) or abnormally high. The high concentrations may enter the range seen in Waldenstrom's macroglobulinaemia. Since the reporting of two cases associating SS and Waldenstrom's macroglobulinaemia (Talal *et al.*, 1967), two further patients have been studied at our institute:

Case 5. *V.B.* (07-90-28)

This 57-year-old Negro woman developed rheumatoid arthritis in 1957. In 1965 she noted the onset of stinging and burning of her eyes, accompanied by lacrimal gland swelling. Lacrimal gland biopsy revealed diffuse lymphoid infiltration. At that time total serum protein was 7·3 g% with 2·6 g% γ-globulin. In July 1967 splenomegaly was noted. In October 1967 she developed weakness and mouth dryness. Bone marrow aspiration demonstrated sheets of mature lymphocytes, and serum proteins included 3·1 g% of a 19S macroglobulin. Chlorambucil, 6 mg daily, was instituted.

On Clinical Center admission in July 1968 the patient had thyroid nodules and hepatosplenomegaly but no significant adenopathy. WBC was 7500 with 10% lymphocytes and

8% monocytes. Total protein was 7·0 g% with 1·1 g% γ-globulin. Rheumatoid factor was absent. Serum IgM was 12·3; IgG, 7·0; and IgA, 3·6 mg/ml. Schirmer's test was positive in both eyes. Rheumatoid changes were evident on wrist X-rays. Lip biopsy demonstrated chronic sialadenitis. *In vitro* tissue culture studies demonstrated local synthesis of a monoclonal IgM paraprotein by lip and bone marrow (Talal *et al.*, 1970). The thyroid nodules were excised and showed focal lymphocytic thyroiditis and nodular fibrosis with osseous and bone marrow metaplasia.

On chlorambucil and 10 mg prednisone, the patient has subsequently done well with considerable improvement in joint symptoms and nearly complete resolution of xerophthalmia and xerostomia. On her latest admission, parotid salivary flow and parotid technetium uptake by sequential salivary scintigraphy were normal. Lacrimal flow continued to be low by Schirmer's test. The most recent serum IgM level was 4 mg/ml.

Case 6. *H.S.* (08-61-54)

Twelve years ago this 59-year-old white woman developed fatigue, arthralgia, and intermittent swelling of the right parotid gland which was subsequently excised. Histology showed benign lymphoepithelial proliferation. In 1963 she was hospitalized for extreme mouth dryness and purpura of the legs. Total serum protein was elevated to 9·9 g%, with 7·5 g% globulins. A mixed 19S–7S cryoglobulin was present in large quantities. Her chest film was abnormal for the first time with increased markings in both lung fields. In 1965 she developed dry eyes, left parotid swelling, and exertional dyspnea. Chest film demonstrated increased diffuse interstitial pulmonary thickening, and pulmonary function studies were abnormal. Rheumatoid factor titre was 1:5120. By early 1970 the patient had become severely dyspneic, with progressive radiologic worsening of interstitial disease.

On her first Clinical Center admission in September 1970, the patient was found to be wasted, chronically ill, and tachypneic, with no significant adenopathy or hepatosplenomegaly. Pulmonary function studies indicated moderately severe restrictive lung disease and hypoxia. An open lung biopsy revealed extensive infiltration of the interstitium with plasma cells and lymphocytes. Amyloid was present in nodules and scattered vessels. Lip biopsy also showed amyloid in addition to marked lymphocytic and plasmacytic infiltration with salivary gland atrophy.

In October 1970, following recovery from post-thoracotomy pneumonia and tracheostomy, the patient received prednisone, 60 mg every other day. Upon follow-up admission 2 months later, her symptoms were markedly improved, and the chest radiograph showed diminished interstitial markings. The IgM has decreased from 11 to 5 mg/ml.

Three more cases of coexistent SS and macroglobulinaemia appear in the literature. Whitehouse *et al.* (1967) described a 54-year-old man with SS, rheumatoid arthritis, lymphocytic pulmonary infiltrates and vasculitis, with later appearance of macroglobulinaemia and eventual death with diffuse interstitial fibrosis. Maleville *et al.* (1967) observed, in the course of SS in an 80-year-old woman, the appearance of a cryomacroglobulin and a β-globulin spike on electrophoresis, which disappeared on steroid therapy and reappeared when steroids were stopped. Post-mortem examination demonstrated a malignant plasma cytic infiltration in lymph nodes, spleen, bone marrow, and liver. Pinkus & Dekker (1970) reported a 59-year-old woman with SS and Waldenstrom's macroglobulinaemia.

Table 1 summarizes the thirty-four reported cases of coexistent SS and lymphoproliferative

disorders and four cases of malignant lymphoproliferation following benign epithelial lesions of the parotid glands.

TREATMENT OF LYMPHOPROLIFERATION ASSOCIATED WITH SJÖGREN'S SYNDROME

There has been no controlled study of the efficacy of any therapeutic agent for the sicca complex. To date, uncomplicated SS has generally been managed conservatively with

TABLE 1. Cumulative review of coexistent Sjögren's syndrome (SS) or benign lymphoepithelial lesions (BLL) and lymphoproliferative disorders

Coexistent disorders	Number of cases	References
SS–Pseudolymphoma	2	Cases 1 and 2
	4	(Talal *et al.*, 1967)
	1	(Tkac *et al.*, 1967)
	1	(Sage & Forbes, 1968)
Total	8	
SS–Stem Cell Lymphoma or Reticulum Cell Sarcoma	1	Case 3
	2	Cases H.H. and A.S. from (Talal *et al.*, 1967), follow-up reported here
	1	(Rothman *et al.*, 1951)
	3	(Talal & Bumin, 1964)
	1	(Talal *et al.*, 1967)
	1	(Hornbaker *et al.*, 1966)
	1	(Miller, 1967a)
BLL–Reticulum Cell Sarcoma	2	(Bark & Perzik, 1968)
	1	(Pinkus & Dekker, 1970)
Total	13	
SS–Malignant Lymphocytic Lymphoma	1	Case 4
SS–Thymoma	1	(Lattes, 1962)
	1	(Dourov *et al.*, 1968)
BLL–Thymoma	1	(Pinkus & Dekker, 1970)
SS–Giant Follicular Lymphoma	1	(Senti *et al.*, 1964)
SS–Lymphosarcoma	1	(Dameshek, 1965)
	1	(Bilder & Hornova, 1967)
	1	(Thorpe, 1969)
SS–Hodgkin's	1	Cited in (Talal & Bunim, 1964)
SS–Lymphoma of Vocal Cords	1	(Yoshinaga, 1968)
Total	10	
SS–Waldenstrom's Macroglobulinaemia	2	Cases 5 and 6
	2	(Talal *et al.*, 1967)
	1	(Whitehouse *et al.*, 1967)
	1	(Maleville *et al.*, 1967)
	1	(Pinkus & Dekker, 1970)
Total	7	

artificial tears and supplemenal oral fluids, which presumably do not alter the process of progressive lymphoproliferation and glandular destruction.

In view of the apparent propensity to extraglandular and even malignant lymphoproliferation in this disorder, a major therapeutic problem is when to initiate anti-lymphoproliferative therapy. If extraglandular lymphoproliferation is recognized at an early stage and if the infiltrating lymphoid cells appear histologically benign, the infiltrate will generally regress on radiation, corticosteroid, or immunosuppressive therapy, with resultant diminished adenopathy or return of normal organ function. If treatment is discontinued, the lesions may recur, and some may progress to frankly malignant lymphomas which are highly resistant to therapy. Of the original six patients with pseudolymphoma described (Talal *et al.*, 1967), there is only one survivor (D.K.). Two (H.H. and A.S.) progressed to fatal reticulum cell sarcoma, as noted above. Another (I.W.), who has also been reported elsewhere (Deutsch, 1967), died of carcinoma of the pancreas. A fourth (L.B.R.) had pulmonary infiltrates and macroglobulinaemia which responded to corticosteroids. She died of vasculitis and pneumonia, with no evidence of pseudolymphomatous pulmonary disease or any notable lymphoreticular disease other than nonspecific lymph node hyperplasia at postmortem examination. The cause of death is unknown in the remaining case (L.S.). While the prognosis in patients with 'pseudolymphoma' must be considered guarded, we feel that early diagnosis and institution of therapy may diminish or at least arrest the lymphoproliferative process and lead to symptomatic improvement and prolongation of life. Radiation therapy is generally not advised in view of the high incidence of prior irradiation in patients who have had lymphoproliferative malignancies.

Immunosuppressive therapy has been successful in some of our patients either in diminishing extraglandular lymphoid infiltrates or in relieving severe symptoms of the sicca complex, or both. One patient treated with chlorambucil (V.B., Case 5) and another with cyclophosphamide (T.J., Case 4) for associated malignancy, each noted marked improvement of xerostomia and xerophthalmia subsequent to treatment. Two patients (M.O. and N.L.) treated with cyclophosphamide for systemic lupus erythematosus and nephritis associated with the sicca complex, each noted concomitant improvement in lacrimal and salivary glandular function (Steinberg & Talal, 1971). Low dose (75 mg daily) cyclophosphamide in another patient (F.E.) with painful bilateral parotid swelling reduced parotid size to normal within a month. The patient noted improvement of xerostomia and xerophthalmia during the second month of treatment. Parotid salivary flow was detectable for the first time on the fifteenth treatment week and was within normal limits during the twentieth week. Demonstrating complete absence of parotid technetium uptake prior to treatment, sequential salivary scintigraphy showed detectable uptake 6 weeks after cyclophosphamide and dramatically improved salivary function by the fifteenth week (Schall *et al.*, 1971).

Other patients with sicca complex have failed to improve with cyclophosphamide. While her pseudolymphomatous renal disease responded well to cyclophosphamide, R.G. (Case 2) continues to experience severe dry eyes and dry month. Two patients treated for associated severe neuropathy (V.M. and E.L.), one for myopathy (M.R.), and one for primary biliary cirrhosis (S.D.) have had no significant subjective or objective improvement in glandular function.

In view of its life-threatening complications, immunosuppressive therapy has generally been reserved for patients with life-threatening or life-crippling diseases. Thus far there have been no significant complications of low-dose cyclophosphamide in a limited number

of patients in our hands, but the safety and efficacy of this therapeutic regimen must be demonstrated by appropriately controlled trials before its use in SS can be recommended. Indications for immunosuppressive agents based on specific criteria of disease activity must also be established.

ANALOGOUS LYMPHOPROLIFERATION IN OTHER DISEASE STATES

The experience of lymphoproliferation occurring in patients with SS may be compared with the observation of similar lymphoproliferation in other autoimmune diseases, in certain immune deficiency states, in patients receiving certain anticonvulsants, and in experimental animal models.

Lymphoproliferation in other autoimmune diseases

Nosancheck & Schnitzer (1969) recently reviewed and emphasized the findings of lymphadenopathy and severe reactive follicular hyperplasia in lymph node biopsies in patients with rheumatoid arthritis and warned against erroneous diagnoses of malignancy in such benign lymphoproliferative processes. Cammarata, Rodman & Jensen (1963) reported convincing evidence of both rheumatic disease and malignant lymphoma in four patients. The coexistence of lymphoproliferative neoplasms and autoimmune disease other than SS has subsequently been the subject of several reports (Fudenberg, 1966; Calabro, 1967; Miller, 1967a; Smith, Cassidy & Bole, 1970).

Antecedent rheumatoid arthritis has existed in patients who have developed giant follicular lymphoma (Cammarata *et al.*, 1963), lymphosarcoma (Miller, 1967a), reticulum cell sarcoma (Miller, 1967a; Goldenberg, Paraskevas & Israels, 1969), chronic lymphocytic leukaemia (Miller, 1967a), Waldenstrom's macroglobulinaemia (Miller, 1967a; Zawadski & Benedek, 1969; Goldenberg *et al.*, 1969), and multiple myeloma (Zawadski & Benedek, 1969; Goldenberg *et al.*, 1969). Other paraproteinemias such as heavy chain disease and benign monoclonal gammopathy have also been reported in association with rheumatoid arthritis (Zawadski *et al.*, 1969; Zawadski & Benedek, 1969). Patients have been reported associating systemic lupus erythematosus with Hodgkin's disease (Cammarata *et al.*, 1963; Howqua & Mackay, 1963; Nilsen, Missal & Condemi, 1967; Miller, 1967a), lymphosarcoma (Howqua & Mackay, 1963; Cammarata *et al.*, 1963), reticulum cell sarcoma (Cammarata *et al.*, 1963), other lymphoma (Dubois & Tuffanelli, 1964; Smith *et al.*, 1970), chronic lymphocytic leukaemia (Miller, 1967a), and acute myeloblastic (Deaton & Levin, 1967) and lymphocytic (Joseph *et al.*, 1970) leukaemia. Hodgkin's disease has also been reported in a patient with dermatomyositis (Miller, 1967a), which is well recognized to be associated with other kinds of malignancy (Williams, 1959; Calabro, 1967).

By an analytic review of series with reported mortalities, Oleinick (1967) found no evidence of increased susceptibility to leukaemia or lymphoma in patients with systemic lupus erythematosus or rheumatoid arthritis. On the other hand, there is a suggestive increase in rheumatoid arthritis (Goldenberg *et al.*, 1969) and diffuse connective tissue diseases (Lea, 1964; Miller, 1967a) in patients with lymphoma. A problem with such epidemiologic studies is that autoimmune disease and malignant lymphoma may resemble each other clinically, histologically, and serologically (Davis, Weber & Bartfield, 1957; Howqua & Mackay, 1963; Miller, 1967a), confusing the diagnosis.

Lymphoproliferation in immune deficiency states

There also appears to be an increased incidence of lymphoproliferative malignancies in certain heritable immunologic deficiences (Fudenberg, 1966; Fraumeni & Miller, 1967; Miller, 1967b). Development of malignant lymphoma and leukaemia has been reported in patients with congenital (Bruton X-linked) agammaglobulinaemia, in which there is a deficiency in humoral immunity, as well as in patients with adult hypogammaglobulinaemia (Page *et al.*, 1963). In ataxia telangiectasia, with impairment of both humoral and cellular immunity (Leiken, Bazelon & Park, 1966; Oppenheim *et al.*, 1966), there have been several reported patients with associated Hodgkin's disease, reticulum cell sarcoma, lymphosarcoma, and leukaemia (Peterson, Kelly & Good, 1964; Peterson, Cooper & Good, 1965; Hecht *et al.*, 1966; Miller, 1967b). Impaired cellular immunity is a feature of Wiskott-Aldrich syndrome (Cooper *et al.*, 1964; Oppenheim, Blaese & Waldmann, 1969), also associated with malignant lymphoma, malignant reticulo-endotheliosis, and leukaemia (Pearson *et al.*, 1966; ten Bensel, Stadlan & Krivit, 1966). Patients with Chediak-Higashi syndrome also appear to be predisposed to lymphoma (Efrati & Jonas, 1958; Page *et al.*, 1962; Dent *et al.*, 1966).

The development of malignant lymphomas in patients with 'acquired' immune deficiency states as a result of immunosuppressive therapy following transplantation has also raised concern. Reticulum cell sarcoma (Doak *et al.*, 1968; Deodhar *et al.*, 1969; Woodruff, 1969; Penn *et al.*, 1969; Starzl *et al.*, 1970), plasmacytoma, and lymphosarcoma (Penn *et al.*, 1969) have complicated renal transplantation in patients treated with azathioprine, prednisone, and/or antilymphocyte globulin.

Lymphoproliferation associated with anticonvulsant drugs

The growing experience of pseudolymphoma and true lymphoma associated with diphenylhydantoin and other anticonvulsant drugs has largely paralleled the experience with this complication of SS. In 1959 Saltzstein & Ackerman (1969) first reported that hydantoin drugs may cause lymphadenopathy that mimics lymphoma. Since the adenopathy usually regressed after the withdrawal of the offending drug, such lymphoproliferation was called pseudolymphoma. In 1962, however, it was reported that two of the initial seven patients with pseudolymphoma had gone on to develop true malignant lymphomas (Harrington, Kissaine & Saltzstein, 1962). Subsequently over 100 cases of pseudolymphoma and lymphoma associated with anticonvulsant drugs have been reported (Hyman & Sommers, 1966; Gama, Neals & Conrad, 1968; Bercel & Henstell, 1970; Anthony, 1970; McGee & Singh, 1970).

The spectrum of lymphoproliferation seen in some patients taking anticonvulsants is remarkably similar, both clinically and histologically, to that observed in SS. Gams *et al.*, (1968) have grouped the hydantoin-induced lymphadenopathy into four categories: (1) *Hyperplasia.* Lymph node biopsy demonstrates a pleomorphic cellular response but no disturbance of normal architecture. (2) *Pseudolymphoma.* Histologically, there are disturbances of normal lymph node architecture and reticulum cell hyperplasia which appear almost frankly malignant. In each of these first two groups, following cessation of hydantoin therapy, lymphadenopathy regresses and does not recur unless therapy is reinstituted. (3) *Pseudo-pseudolymphoma.* Initially indistinguishable from the first two groups, clinically and histologically, patients in this third group experience an asymptomatic quiescent period

after withdrawal of the drug but then go on to develop a frankly malignant lymphoma and die. (4) *Lymphoma.* Patients in this group pose no clinical or histologic diagnostic problem and present initially as obvious Hodgkin's disease, reticulum cell sarcoma, or lymphosarcoma. Patients with adenopathy and SS could be similary categorized; for example, A.S. and H.H. described earlier could be regarded as having had 'pseudo-pseudolymphoma'.

Lymphoproliferation in experimental animal models

Widespread immunoproliferation and a tendency to develop lymphoid or plasma cell neoplasms, analogous to patients with SS, have been observed in three animal models: New Zealand Black mice, Aleutian mink, and allogeneic disease in mice, all recently reviewed (Schwartz & Andre-Schwartz, 1968).

New Zealand Black mice (NZB). NZB mice spontaneously develop an autoimmune disorder characterized by autoantibody formation, haemolytic anaemia, nephritis (Howie & Helyer, 1968), and salivary gland infiltrates (Kessler, 1968) resembling those in SS. These mice have abnormalities of both humoral and cellular immunity. They make excessive antibody responses to certain antigens and are relatively resistant to the induction of immunological tolerance (Staples & Talal, 1969). Cellular immunity, as measured by the graft-vs-host reactivity, tumour rejection, and response to phytohaemagglutinin, is depressed (Cantor, Asofsky & Talal, 1970; Leventhal & Talal, 1970).

In addition to autoimmune disease, NZB mice develop lymphoid, plasma cell, and reticulum cell hyperplasia; they produce high levels of macroglobulins; and one-fifth to one-third develop lymphoid malignancies (Holmes & Burnet, 1963; East, de Sousa & Parrot, 1965; Mellors, 1966). Transplantation of lymphoid tissue undergoing extensive proliferative reactions to young syngenic mice produces lethal reticulum cell sarcoma (East *et al.*, 1967).

The pathogenesis of autoimmunity and lymphoma in NZB mice involves genetic, viral, and immunologic factors (Talal, 1970). The genetic predisposition to the disorder can be modified or suppressed in heterozygote offspring by factors introduced through mating with other strains such as New Zealand white or C_3H (Holmes & Burnet, 1964). The naturally occurring murine leukaemia virus, other viruses, and even synthetic double-stranded nucleic acids will accelerate autoimmunity in these mice (Steinberg, Baron & Talal, 1969). Depressed cellular immunity and impaired immunologic surveillance may permit unusual expressions of viral infection, such as autoimmunity, lymphoproliferation, and malignant lymphoma.

Aleutian mink disease. Genetic, viral, and immunologic factors may also play a role in the development of Aleutian mink disease. Mink homozygous for a recessive mutant gene *a* affecting fur colour have a high incidence of this disease, characterized by anaemia, positive antiglobulin tests, extensive systemic proliferation of plasma cells, massive and diffuse hypergammaglobulinaemia, and fibrinoid vascular lesions with renal disease (Obel, 1959; Wagner, 1963; Thompson & Aliferis, 1964). Transmissibility to normal mink by cell-free extracts of affected mink tissue and the ability to sediment the infectivity by ultracentrifugation strongly suggest a viral etiology (Franglen, 1963). Some mink undergo a transition from diffuse hypergammaglobulinaemia to a homogeneous myeloma-like gammopathy with Bence Jones proteinuria (Porter, Dixon & Larsen, 1965). This animal model, then, is thought to represent a viral disease with plasma cell proliferation initially multiclonal but terminally monoclonal, possibly as a result of neoplastic overgrowth of the plasma cell system (Porter

et al., 1965). Similar antiglobulin activity and hypergammaglobulinaemia, progressing in some instance to monoclonal gammopathy, are seen in SS.

Allogeneic disease. A marked proliferative reaction in spleen and lymph nodes and subsequent development of malignant lymphoma, comparable to that described in SS, have been observed in mice with chronic graft-vs-host reaction (GVHR) or allogeneic disease (Schwartz & Beldotti, 1965). GVHR is induced by the administration of foreign, immunologically competent lymphoid cells to an animal who cannot reject them. Schwartz & Beldotti (1965) produced chronic allogeneic disease by injecting (C57BI/6 × DBA/2) F_1 hybrid mice with spleen cells from their inbred parental lines (C57BI/6), which mounted a reaction against the DBA/2 antigens in the host, resulting in GVHR. One-third of the surviving recipient animals developed lymphoma. Since impaired immune responses are a feature of acute (Schwartz *et al.*, 1966) and possibly chronic GVHR, Schwartz & Andre-Schwartz (1968) suggested that the immunodepressive effects of the GVHR may permit the growth of a line of virus-containing neoplastic cells. Subsequently it was shown that inoculation of parental BALB/c spleen lymphoid cells into young adult (BALB/c × A/J) F_1 hybrid mice results both in a sustained immunoproliferative reaction with a high incidence of reticulum cell sarcoma (Armstrong *et al.*, 1970) and activation of leukaemia viruses (Hirsch *et al.*, 1970).

THEORIES REGARDING THE ASSOCIATION OF LYMPHOPROLIFERATION WITH AUTOIMMUNE DISEASE AND IMMUNE DEFICIENCY

At this point in our knowledge there is no adequate explanation for the lymphoproliferation in glandular tissue and its spread to extraglandular sites, the autoimmune phenomena, or the tendency for lymphoreticular malignancy in SS. The overlap of autoimmune disease, immune deficiency, and/or lymphoma has generated several theories, not necessarily mutually exclusive: (1) chronic intense stimulation to the immune system in autoimmune disease leads to lymphoma (Dameshek & Schwartz, 1959; Talal & Bunim, 1964; Miller, 1967a); (2) neoplastic lymphocytes arising from 'forbidden clones' (Burnet, 1959) are responsible for the autoimmune disease; (3) impairment of normal host defence mechanisms, or immunologic surveillance, permits either the growth of abnormal cells or the unusual expression of viral infection; (4) an individual patient is genetically susceptible to both immune and malignant disease (Miller, 1967a); (5) a common stimulus, such as a virus, is responsible for both autoimmune and malignant disease; and (6) the relationships are coincidental.

(1) *Chronic intense stimulation.* The point has already been made that the prominence of lymphocytic infiltration, the hypergammaglobulinaemia, the high incidence of autoantibodies, and the local excessive synthesis of immunglobulins in the lip all suggest intense, active stimulation of the immune system in SS, even in the 'benign' stage of the disease. The stimulus initiating the process remains unknown but presumably in some way could alter 'self' antigens which then evoke an immune response. For instance, latent viral infection of the ductal epithelial cell may result in an antigenic alteration of the cell membrane, provoking a humoral (antisalivary duct antibody) or cellular (lymphocytic infiltrate) immune response. On persistent stimulation and immunoproliferation, the process initiated in the glandular tissue may manifest itself systemically, e.g. by hypergammaglobulinaemia or by eventual spread of lymphoid infiltration to extraglandular sites. At some stage of chronic stimulation,

the involved immunocytes could undergo neoplastic transformation, either to hyperfunctioning, paraprotein-producing cells (macroglobulinaemia) or, by 'exhaustion atrophy' and dedifferentiation, to primitive blast cells (reticulum cell sarcoma).

There is some suggestion that protracted antigenic stimulation of the reticuloendothelial system by desensitization procedures may result in the development of a single clone of paraprotein-producing cells, giving rise to myeloma or macroglobulinaemia (Penny & Hughes, 1970). The recent emphasis on the likelihood that lymphoreticular hyperplasia and general immunoproliferation resulting from malaria infection predispose to the induction of Burkitt's lymphoma (O'Conor, 1970; Lancet editorials, August 8, 1970 and September 19, 1970) is also noteworthy.

Animal models support the concept of the oncogenic effect of persistent immunologic stimulation, as already discussed for NZB mice (Mellors, 1966), Aleutian mink disease (Porter *et al.*, 1965), and allogeneic disease of mice (Schwartz & Beldotti, 1965; Schwartz & Andre-Schwartz, 1968). Also, Metcalfe (1961) and others have induced reticular neoplasms in C_3H and other strains of mice by repeated injections of bovine serum albumin and assorted antigens.

(2) *Primarily neoplastic immunocytes, with secondary autoimmunity.* There are several ways in which a primary process of neoplasia could conceivably result in autoimmune phenomena. Normal 'self' antigens may be the targets of abnormal immunocytes (Dameshek, 1965) arising from 'forbidden clones' (Burnet, 1959) which result from genetic predetermination or somatic mutation. The accelerated rate of neoplastic cell division could provide increased opportunity for somatic mutation to form cell lines capable of reacting immunologically against normal tissue antigens (Cammarata *et al.*, 1963). Another possibility, proposed by Fudenberg (1966), is that mutation gives rise to cells which are antigenically deficient and thus not recognized as foreign. Such mutant cells would then survive normal immunologic surveillance mechanisms (third hypothesis) and proliferate. If the mutant cells recognize normal tissue as foreign and mount an immunologic reaction against it, as in graft-vs-host disease, 'autoimmunity' could result. Still another possibility is that primarily malignant cells cause tissue destruction and immunologic alterations of normal tissue that somehow trigger an autoimmune response.

Miller (1967a) argued that if neoplastic lymphocytes are responsible for the immune disorders, one would expect the malignant lymphoma to precede the immune disease, but the temporal relationship of the detection of these two disorders in individual patients is often just the opposite. As noted earlier, typical sicca complex may precede malignancy in patients with SS by 15 years or more.

(3) *Impaired immunologic surveillance.* An important feature of SS shared by other human and animal disease states with increased incidence of malignancy (ataxia telangiectasia, Wiskott-Aldrich syndrome, immunosuppressed transplant patients, NZB mice, and allogeneic disease of mice) is an apparently depressed state of cellular immunity, as measured by dinitrochlorobenzene sensitization and mitogenic response to phytohaemagluttinin by peripheral lymphocytes (Leventhal, Waldorf & Talal, 1967). Similar impairment of cellular immunity has been observed in patients with primary neoplasms, such as Hodgkin's disease (Hersch & Oppenheim, 1965). Depressed cellular immunity brought about by antilymphocytic serum increases the incidence of polyoma virus oncogenesis and Maloney virus leukaemogenesis in mice (Allison & Law, 1968).

Burnet (1967) has emphasized the essential role of an intact immunologic system to

eliminate 'foreign' malignant cells arising by somatic mutation. Arising in an immunologically-deficient individual, mutant immunocytes could undergo uninhibited proliferation and result in either autoimmune disease or lymphoma or both. Another possibility is that depressed cellular immunity and impaired immunologic surveillance permit unusual micro-organism infection or unusual manifestation of common micro-organism infection which is itself responsible for autoimmunity, lymphoproliferation, and malignant lymphoma.

(4) *Common genetic susceptibility*. As in NZB mice or homozygous *aa* Aleutian mink, humans with autoimmune or congenital immune deficiency disease may represent specific genotypes which are also susceptible to the development of malignancy. The common denominator may be a genetically determined immunologic abnormality (Miller, 1967b), as in the third hypothesis. The increased incidence of lymphoma and leukaemia in other human genetic disorders, such as Down's syndrome, Klinefelter's syndrome, D-trisomy, Bloom's syndrome, and Fanconi syndrome, has also been noted (Miller, 1967b; Fraumeni & Miller, 1967). Detailed studies of the incidence of autoimmune phenomena or lymphoma among families of patients with SS are not available.

(5) *A common stimulus*. There is mounting evidence that viruses may play a role in certain human autoimmune diseases, such as systemic lupus erythematosus (Talal, 1970), which has also been linked with lymphoid neoplasms. Viral-like particles have been demonstrated in the kidneys from two patients with SS (Shearn *et al.*, 1970). To date, attempts to isolate a viral agent or to demonstrate viral antigens in salivary glands or lymph nodes from patients with SS have failed. However, experience with other latent viral infections of man, such as Kuru or subacute sclerosing parencephalitis, suggest that continued attempts at viral isolation are warranted.

The evidence has already been cited that viruses may play a role in NZB mice and Aleutian mink disease, which manifest both autoimmune and neoplastic disease. In another animal model, reovirus 3 is capable of inducing both diseases in PH mice, the one characterized by autoimmune runting and lymphoid atrophy, resembling a graft-vs-host reaction, and the other a malignant lymphoma, resembling Burkitt's lymphoma (Stanley & Walker, 1966).

(6) *Coincidental coexistence*. Epidemiologic studies to demonstrate statistic significance of coexisting SS and lymphoma are wanting, but it seems unlikely that the two disorders, as reported, have occurred in the same patients by chance alone.

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